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REVIEW ARTICLE

Genetic Backgrounds of Asthma and COPD

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ABSTRACT

Asthma and COPD are complex diseases with strong genetic and environmental components. These common pulmonary diseases have both different and similar clinical features. Molecular genetic techniques are being used to improve understanding of these common late onset disorders. Recently, several genes and genetic loci associated with increased susceptibility to asthma and COPD have been described. Many of these genes are expressed in the lung tissues, indicating that events in lung tissues might drive disease processes. Lung tissues are rich sources of innate danger signals, and an increased understanding of how the lung tissues communicate with the immune system to maintain healthy tissue might provide new insights into the pathogenesis of chronic inflammatory lung diseases in which injury and repair are in disequilibrium. Given that the innate immune system is at the interface between the airways and environmental insults, genetic polymorphisms in genes related to the innate immune system are likely to affect susceptibility to both asthma and COPD. In addition, some findings from genetic studies provide molecular support for the point of view proposed in the Dutch hypothesis regarding the relationship between asthma and COPD, which highlights the complexity of the pathways that can induce small airway disease and suggests that there is a continuum between asthma and COPD.

KEY WORDS

ADAM33, asthma, CCL5, COPD, Dutch hypothesis, IL17F

INTRODUCTION

Both asthma and chronic obstructive pulmonary disease (COPD) are characterized by airflow limitation, airway remodeling and chronic inflammation.[1,2] Genetic factors play an important role in the development of these diseases, which has prompted much research to identify the underlying disease susceptibility genes. Genetics provides a unique tool for studying the pathophysiology of asthma and COPD. Traditional candidate gene studies may focus on a single gene or on a few genes in combination, with these genes identified based on prior knowledge or suspected mechanisms of disease pathogenesis. In contrast, genome-wide linkage and association studies allow for the comprehensive evaluation of the entire genome without prior assumptions regarding disease pathobiology. Nonetheless, elucidating the genetics of these disorders is severely hampered by genetic heterogeneity, the low penetrance of individual disease alleles, and the potential for gene-gene and gene-environment interactions. Hence, it is likely that many different susceptibility alleles contribute to each disease, each of which has only a modest effect.[3]

The primary value of genetic mapping is not risk prediction, but providing novel insights into pathogenesis of disease. Although the significance of association signals have yet to be translated into a full understanding of the genes or genetic elements that mediate disease susceptibility at particular loci, these studies may lead to the identification of novel candidate genes, which can be subjected to further *in vitro* or *in vivo* experimentation. These genes may identify novel pathogenic pathways, which will be targets for therapies or biomarkers for the diagnosis and follow-up of patients with asthma or COPD.[3] Genetic studies also indicate that particular molecular pathways seem to underlie the pathogenesis of both asthma and COPD, which confirms the suggestion that shared

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Gene	Chromosome	Function and pathway	Common variants
GSTM1	1p13.3	Environmental and oxidative stress — detoxification	+/null
FLG	1q21.3	Epithelial barrier integrity	Arg510X, 2282del4
IL10	1q31-q32	Immunoregulation	-1082A/G, -571C/A
CTLA4	2q33	T-cell-response inhibition and Immunoregulation	-318C/T, 49A/G
IL13	5q31	T_H2 effector functions	-1112C/T, Arg130Gln
IL4	5q31.1	T_H2 differentiation and IgE induction	-589C/T, +33C/T
CD14	5q31.1	Innate immunity — microbial recognition	-1721G/A, -260C/T
SPINK5	5q32	Epithelial serine protease inhibitor	Glu420Lys
ADRB2	5q31-q32	Bronchial smooth-muscle relaxation	Arg16Gly, Gln27Glu
HAVCR1	5q33.2	T-cell response regulation — HAV receptor	5383_5397del
LTC4S	5q35	Cysteinyl leukotriene biosynthesis — inflammation	-444A/C
LTA	6p21.3	Inflammation	*Nco*I (intron1)
TNF	6p21.3	Inflammation	-308G/A, -857C/T
HLA-DRB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DQB1	6p21	Antigen presentation	Multi-SNP alleles
HLA-DPB1	6p21	Antigen presentation	Multi-SNP alleles
GPRA	7p14.3	Regulation of cell growth and neural mechanisms	Haplotypes
NAT2	8p22	Detoxification of drugs and carcinogens	Slow acetylation SNPs
FCERIB	11q13	High-affinity Fc receptor for IgE	Ile181Leu, Gly237Glu
CC16	11q12.3-q13.1	Epithelium-derived anti-inflammatory protein	38A/G
GSTP1	11q13	Environmental and oxidative stress — detoxification	Ile105Val
IL18	11q22.2-q22.3	Induction of IFNγ and TNF	-656T/G, -137G/C
STAT6	12q13	IL-4 and IL-13 signalling	2964G/A, (GT)n exon1
NOS1	12q24.2-q24.31	Nitric oxide synthesis — cell-cell communication	3391C/T, 5266C/T
CMA1	14q11.2	Mast-cell chymotryptic serine protease	*Bst*X1, -1903G/A
IL4R	16p12.1-p12.2	α-chain of the IL-4 and IL-13 receptors	Ile50Val, Glu551Arg
CCL11	17q21.1-q21.2	Epithelium-derived eosinophil chemoattractant	Ala23Thr, -1328G/A
CCL5	17q11.2-q12	Monocyte, T-cell and eosinophil chemoattractant	-403A/G, -28C/G
ACE	17q23.3	Inactivation of inflammatoty mediators	In/del
TBXA2R	19p13.3	Smooth-muscle contraction, inflammation	924T/C, 795T/C
TGFB1	19q13.1	Immunoregulation, cell proliferation	-509C/T
ADAM33	20p13	Cell-cell and cell-matrix interactions	Multiple SNPs
GSTT1	22q11.23	Environmental and oxidative stress — detoxification	A/null

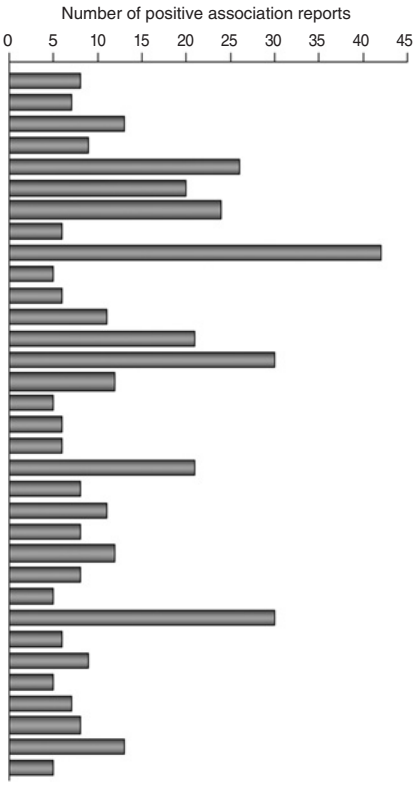

Fig. 1 Susceptibility genes for asthma and asthma-related traits. Summary of the genes that were found to be associated with asthma and/or asthma-related phenotypes in at least five independent reports of candidate-gene association or positional-cloning studies. Adapted from reference 3.

molecular mechanisms that are due to common genetic variants contribute to a spectrum of diseases.

Susceptibility genes almost certainly interact with multiple environmental exposures or stimuli that are important in the etiology of a disease, and these interactions may vary with age, sex, and from one population to another. It is clear that inter-individual variation in response to a given exposure exists across an individual lifetime. Therefore, identification of the host factors that may influence susceptibility to environmental exposures remains an important issue. In terms of asthma and COPD, innate immunity is particularly interesting, as it provides links to environmental triggers of disease and might provide new tools for disease prevention at host environmental interfaces. We therefore can consider the interactions between susceptibility genes and viral infection, cigarette smoking, and allergen exposure as an opportunity to better characterize the plasticity of genetic programs, and to understand how the environment modifies disease susceptibility.

This review discusses the contribution of genetics to the understanding of asthma and COPD and specifically focuses on the hypothesis that asthma and COPD share some pathogenic mechanisms as originally proposed in 1960 in a theory that has since become known as the Dutch Hypothesis.[4]

GENETICS OF ASTHMA

The search for asthma susceptibility genes has been an area of intense investigation. Two general approaches have been widely used to study the genetics of asthma: candidate gene association studies and, more recently, genomewide linkage or association studies followed by positional cloning.[3] Using candidate gene association studies, more than 100 candidate genes have been studied because their biological function suggests that they could play a role in the pathogenesis of asthma[3] (Fig. 1). Until recently, most of the association studies in asthma and allergy were based on genes involved in T-cell signaling and the adaptive immune responses. Although much of the evidence demonstrates continuous involvement of Th2-type T-cell-mediated processes in established disease, it is clear that many other processes contribute to disease pathology, and the disease probably exhibits several heterogeneous phenotypes.[5] Overall, genome-wide linkage and association analyses have kept their promise. Indeed, their results have renewed the interest of asthma researchers in host environmental interfaces such as the epithelium, the smooth muscle, and the fibroblast, which are at the

core of the organ-specific component of asthma pathogenesis, but had been neglected by association studies. For example, *DPP10* and *GPRA*, two genes that have been positionally cloned for asthma, are strongly expressed in the respiratory epithelium, indicating that the importance of epithelial defense in the pathogenesis of asthma.[6,7]

The results of the first, and so far only, genome-wide association study for asthma were published in 2007.[8] In the discovery phase of the study, 317,000 single nucleotide polymorphisms (SNPs) were typed in 994 patients with childhood-onset asthma, resulting in the identification of a novel locus on chromosome 17q12-q21 containing multiple genes and associated markers. The association between the 17q21 locus and diagnosis of childhood asthma was independently replicated in 2,320 subjects from a cohort of German children and in 3,301 subjects from the British 1958 birth cohort.[8] The region of association on chromosome 17q21.1 spanned 206 kb and included 19 annotated genes. Expression analysis in lymphoblastoid cell lines revealed that *ORMDL3* expression was strongly correlated with asthma-associated variants in the region, leading the authors to conclude that it was the most likely candidate gene at this locus. Another large, family-based genetic study that included extensive phenotypic and environmental data showed that the increased risk of asthma conferred by 17q21 is restricted to early-onset asthma and that the risk is further increased by early-life exposure to environmental tobacco smoke.[9] In a Japanese population, a significant association was also found between susceptibility to childhood asthma and the polymorphism regulating *ORMDL3* expression.[10] It is of note that these studies consistently failed to find a significant association between the *ORMDL3* SNPs and atopy or total serum IgE levels.[11] This disjunction implies that atopy does not drive the underlying disease process of asthma, even in early childhood. In contrast, in normal human lung fibroblasts, the expression level of *ORMDL3* was strongly induced by stimulation with polyinosine-polycytidylic acid [Poly (I: C)]. These findings suggest an important role of the highly induced ORMDL3 in viral respiratory infections[10]; in susceptible individuals, some viruses may elicit an aberrant or disproportional response of fibroblasts, resulting in significant airway pathology in the host.

GENETICS OF COPD

COPD is also influenced by multiple genetic determinants, but severe α1-antitrypsin deficiency is the only proven genetic risk factor.[12] Given the clear role of smoking in this disease and the inter-individual differences in response to cigarette smoke,[13] COPD etiology is expected to include gene-environment interactions.

Numerous candidate genes that could be linked to disease pathogenesis have been implicated in COPD genetics.[14] These studies have provided evidence for the possible role of many inflammatory mediators and their receptors, proteases, antiproteases, and antioxidant and xenobiotic genes in COPD pathophysiology. For example, a systematic review of the literature characterized the evidence that genes coding for antioxidant enzymes contribute to the etiology of COPD and related traits; the strongest and most consistent effects were in the genes encoding glutamate-cysteine ligase (GCL), glutathione S-transferase M1 (GSTM1), glutathione S-transferase P1 (GSTP1), and superoxide dismutase 3 (SOD3).[14,15]

Genome-wide association studies offer the prospect of identifying new genes involved in COPD susceptibility and genetic modifiers of disease phenotypes. Genomewide linkage analysis of the Boston Early-Onset COPD Study families using pulmonary function phenotypes demonstrated a significant linkage peak on chromosome 2q.[16-18] Using expression-array analysis of murine and human lung tissues, Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2 (*SERPINE2*) has been identified as a novel candidate COPD-susceptibility gene on chromosome 2q.[19] SERPINE2 was expressed highly in the developing mouse lung during alveogenesis, and that it was also expressed in airway epithelial cells and vascular adventitia of adult human lungs,[19] implying that this molecule may be involved in the pathways of lung development, tissue remodeling, and repair in the lungs.

THE DUTCH HYPOTHESIS

Asthma and COPD show similarities, transitions, and substantial differences[1,2]; a significant number of patients with obstructive airway disease exhibit physiologic and pathologic characteristics of both classical asthma and COPD. Although these common diseases may occur concurrently in some patients, this might reflect common mechanisms between asthma and COPD that are related to intrinsic determinants of disease pathogenesis.[20]

The Dutch hypothesis considers asthma and COPD a single entity whose pathogenesis involves environmental and host factors.[21] It suggests that genetic factors (eg, airway hyperresponsiveness and atopy),[22] endogenous factors (eg, sex and age), and exogenous factors (eg, allergens, infections, and smoking) all play a role in the pathogenesis of chronic nonspecific lung disease. A simple model is that exposure to environmental risk factors in a genetically susceptible host leads to a disease. A particular combination of genetic and environmental risk factors leads to one disease, and another combination of factors leads to a different disease.

The innate immune axis is activated in the lungs of humans with chronic airway disease due to asthma or COPD,[23,24] demonstrating the importance of the ex-

ternal environment such as infectious agents, airborne oxidant gases, and particulates. Infections and occupational and environmental stimuli (allergic and nonallergic) cause repeated bouts of inflammation and contiguous repetitive engagement of different components of the immune system in the lung. The resulting interactions with genotype may give rise both to distinct disease phenotypes and to individual variations in disease presentation and progression. For example, abnormal phenotypes of cytokine generation and responsiveness to inflammatory insults of airway epithelium and smooth muscle in asthma or COPD can result from many underlying genetic factors influencing the macrophage, epithelium, and smooth muscle. Alterations in the proportions of tissues and innate immune cells available to respond to stimuli, as well as their temporal and spatial location within the airways, will further influence differential responses to repeated insults.

The genetic association of the same common polymorphisms with asthma and COPD points to a shared molecular cause. In the following section, three genes are discussed as examples of shared genetic components for both asthma and COPD, including genes encoding ADAM33, CCL5, and IL17F.

ADAM33

A disintegrin and metalloproteinase 33 (*ADAM33*) is the first positionally cloned asthma gene.[25] The linkage analysis that led to the identification of *ADAM33* as an asthma susceptibility gene was conducted on 460 affected Caucasian families from the United Kingdom and United States. Significant linkage to asthma and bronchial hyperresponsiveness was identified in chromosome 20p. Further high-resolution SNP analyses identified *ADAM33* as the source of the linkage signal. The association of *ADAM33* with asthma and lung function has been confirmed in multiple populations with distinct ethnic backgrounds.[26] *ADAM33* is expressed by lung fibroblasts and bronchial smooth-muscle cells, but not by bronchial epithelial cells or immune cells, pointing to potentially new pathogenetic pathways for asthma. *ADAM33* is also preferentially expressed during branching morphogenesis in mouse and human lungs, suggesting a function linked to the role of the epithelial-mesenchymal trophic unit in lung development.[27]

Airway hyperresponsiveness (AHR) is a risk factor for an accelerated decline in forced expiratory volume in 1 second (FEV1) and the development of asthma and COPD, irrespective of atopic status.[22] Indeed, some of the SNPs of *ADAM33* were shown to be significantly associated with the development of COPD and annual lung function decline in a general population.[28,29] Thus, genetic factors driving AHR may allow for the development of asthma and COPD, proving the existence of genetic links between these two diseases.

Based on the findings of *ADAM33* (and also *SERPINE2*), it is conceivable that a program of lung structure maintenance of critical importance during lung development is retained along with preserved architectural building principles, and that, later in life, elements of this developmental program are used to protect the lung against attacks by the innate immune system activated by infections, tissue damage, and antioxidants. Genetic susceptibility to the dysregulation of this program may lead to repair failure, underlying the pathogenesis of asthma and COPD.

CCL5

We previously reported that the gain-of-function-28 G allele of the promoter SNP (rs2280788: –28C > G) in the CC chemokine ligand 5 gene (CCL5) was associated with susceptibility to late-onset asthma in patients who developed asthma at age >40 years.[30] In general, late-onset asthma is not strongly associated with specific allergen sensitisation. Rather, infections, including respiratory viruses, may be more likely to be involved in the pathophysiology of late-onset asthma through host response mechanisms.[31] Viral infections are associated with most exacerbations of asthma and COPD,[32-36] and the most prominent aspect of the epithelial immune response toward viral respiratory infections consists of the production and release of CCL5.[37-40] Indeed, exacerbation of mild COPD is associated with the up-regulation of CCL5 in both inflammatory and epithelial cells of the bronchial mucosa.[39,41] Given that accumulation of inflammatory immune cells and airway wall remodeling processes are common characteristics in the small airways of patients with asthma and COPD,[42] a common genetic susceptibility may be present, with latent viral infections predisposing some patients to experience increased airway inflammation.

CCL5 may be involved in the pathogenesis of epithelial remodeling and chronic hyper-reactivity in response to viral infections. We therefore investigated whether CCL5 has a genetic impact on the variable expression of emphysema in patients with COPD.[43] A total of 267 patients with COPD were studied. All patients underwent pulmonary high resolution computed tomography (CT), and visual scoring (CT score) was performed to determine emphysema severity. Three SNPs of *CCL5* were genotyped, including rs2107538 (–403 G > A), rs280788 (–28C > G), and rs2280789 (375T > C). A significant difference was found in CT score according to *CCL5* genotype: the –28 G allele was inversely associated with CT score ($p = 0.00038$). When the analysis was confined to 180 patients with bronchial reversibility <15%, even stronger evidence for this association was noted ($p = 0.00002$).

The chronic airflow limitation associated with COPD is caused by a mixture of small airway disease and emphysema, the relative contributions of which vary from person to person.[44] These phenotypic vari-

ations of COPD may be influenced by several innate susceptibility factors to environmental stimuli, including tobacco smoking and viral respiratory infections. These phenotypes (small airway disease and emphysema) show independent aggregation within families of individuals with COPD, suggesting that different genetic factors influence these disease processes.[45] CT scans of the chest can be used to confirm the presence and to grade the severity of emphysema, and COPD patients with milder emphysema, despite severe airflow limitation, could be considered as having predominantly small airway disease. Within the context of the previous finding that the −28 G allele was associated with late-onset asthma, the observation of an inverse association between the −28 G allele and CT score in patients with COPD leads to a specific hypothesis that increased severity of small airway disease caused by a gain effect of the −28 G allele may underlie the chronic inflammation and remodeling of the small airways of late-onset asthma and COPD with milder emphysema. The chronic activation of innate immunity to virus infections may also be a part of a common pathway in the pathogenesis of late-onset asthma and COPD with milder emphysema.

IL17F

IL-17 family members belong to a distinct category of cytokines that coordinate local tissue inflammation by inducing the release of pro-inflammatory and neutrophil-mobilizing cytokines. IL-17F is a recently discovered member of the IL-17 family that has a number of biological activities through induction of various cytokines, chemokines, and mediators. IL-17A, the founding member of the IL-17 family, and IL-17F are produced by several inflammatory cells, including activated T cells, in response to infectious and antigenic stimuli. Recent progress in molecular and functional studies of IL-17F has provided evidence for its role in pulmonary neutrophilia through the induction of CXC chemokines.[46]

As the diseases progress and higher doses of corticosteroids are required, the inflammatory patterns of asthma and COPD become harder to distinguish from one another. Increased infiltration of the airway with neutrophils characterizes lung inflammation in COPD and severe asthma[47-49] and, not surprisingly, neutrophilia is often associated with disease severity[50] and chronic airway narrowing.[49] Neutrophils are believed to contribute to tissue damage through the release of granule proteins and reactive oxygen metabolites, as well as pro-inflammatory and pro-fibrotic cytokines. In addition to causing direct tissue damage, neutrophil-derived pro-inflammatory mediators can perpetuate inflammation, resulting in chronic changes in airway function.[51]

To investigate the role of IL-17F in asthma pathogenesis, we conducted genetic analyses of the association of asthma with the common variants of *IL17F*, using 867 unrelated Japanese subjects.[52] Five polymorphisms were studied, including the coding-region sequence variant SNP rs763780 (7488T > C), which causes a His-to-Arg substitution at amino acid 161 (H161R). A genotype-based $\chi 2$ association analysis indicated a significant association between the H161R variant and asthma ($p = 0.0028$). Importantly, none of the asthmatic subjects were homozygous for H161R. The odds ratio (OR) for asthma was 0.06 (95% confidence interval, 0.01-0.43, $p = 0.0039$) among H161R homozygotes compared with wild-type homozygotes. We then combined bronchial asthma and COPD into a single category to examine whether association of this variant with the chronic inflammatory airway disease would be found. When the results were stratified according to atopic status, the H161R variant was significantly associated with the combined disease status, especially among atopic subjects ($p < 0.005$).[53] In atopic patients with asthma, pre-bronchodilator baseline FEV1/forced vital capacity (FVC) values also showed a significant association with the H161R variant ($p = 0.00083$).[53]

In vitro functional studies further demonstrated that, compared with wild-type IL-17F, the H161R variant is unable to activate MAP kinase, as well as cytokine and chemokine production, in bronchial epithelial cells (Fig. 2). Of significance, the H161R variant inhibits induction of IL-8 by wild-type IL-17F. These findings suggest a potential mechanism underlying the significant association observed between the IL-17F H161R variant and asthma and COPD. As chronic inflammation is thought to play a crucial role in deteriorating lung function, IL-17F may serve as a target for ameliorating the effects of neutrophil-mediated chronic airway inflammation.

The impact of a viral infection in atopic subjects on airway inflammation may be influenced by the presence of H161R. A previous study[54] demonstrated increased airway epithelial mucus production among pre-sensitized RSV-infected (OVA/RSV) mice, compared with OVA mice 14 days after infection, whereas almost no mucus production was observed in mice that were only RSV infected. Although they did not find an increase in type 2 cytokine production in OVA/RSV mice compared with OVA mice, they found a significant association between increased gob-5 and Muc5ac expression in OVA/RSV mice and increased IL-17A levels in the lung. Infectious agents can induce inflammatory lung disease akin to asthma and COPD, which include airway inflammation, mucus hypersecretion, and laborious breathing. Virus infection may be the additional event that is required for atopic sensitization to progress to asthma. Moreover, because cigarette smoke induces alterations in the innate immune response to viral infection,[55] chronic virus infection may also determine which smokers are at risk for obstructive airway disease, as

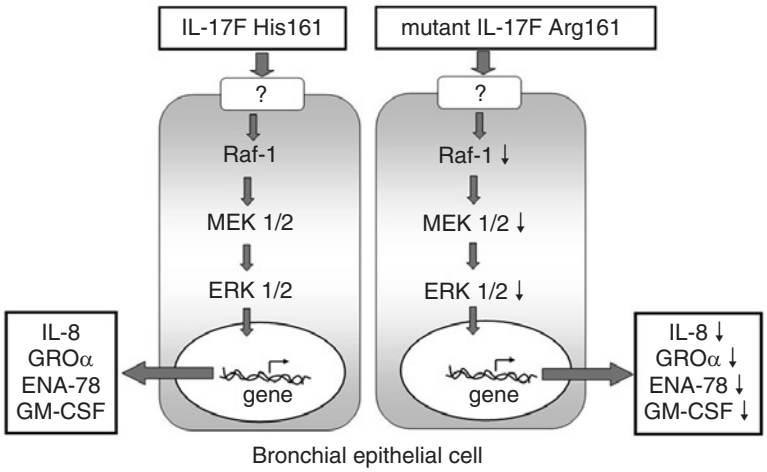

Fig. 2 Proposed functional consequences of the IL17F H161R variant. Mutant IL-17F was unable to activate the Raf1-MEK1/2-ERK1/2 pathway, but antagonized wild-type IL-17F activity, suggesting that IL-17F is able to bind the receptor, but not activate the signalling pathway. Adapted from reference 53.

COPD develops in only a minority (15 to 20%) of current smokers. Thus, our findings regarding the *IL17F* gene may have identified another gene in a common pathway mediating the development of asthma and COPD.

CONCLUSIONS AND FUTURE PERSPECTIVES

The completion of the Human Genome Project, the HapMap project, technological advances in SNP genotyping, and the potential of genome-wide association analysis will allow the identification of susceptibility genes for asthma and COPD. The genetic predisposition to impairment of a certain pathway might help define clinical subgroups of disease and prioritize patient groups for a specific therapy. This review described 3 susceptibility genes that are common for asthma and COPD. These genes support the model of shared genetic risk factors for asthma and COPD and may also help identify previously unexpected biologic pathways that link these two diseases.

The innate immune system can be activated by signals from cells exposed to pathogens, environmental stimuli, or mechanical tissue damage. The presumed function of stress immunosurveillance is to contribute to tissue repair and maintenance by eliminating stressed or damaged cells and facilitating the restoration of healthy cells. In the context of asthma and COPD, the local pulmonary immune system appears to be chronically activated as if it recognizes products of damaged tissues, virus-infected, or smoking-stressed cells. Considering recent results of genetic studies of asthma and COPD, the emerging picture is that aberrant activation of the innate immune system accounts for the findings that inflammation persists and lung function continues to decline in patients with asthma and COPD.

Future research will increase our understanding of both the cellular and molecular mechanisms at work during normal lung function and under conditions in which the lung is exposed to environmental stress. Objective assessment of comprehensive genetic profiles will help identify susceptible individuals who might develop persistent airway inflammation underlying asthma and COPD. Patients with different diseases but overlapping pathways might benefit from the same treatment, which could lead to the development of new and shared therapeutic prospects. Given that many of the clinical and pathological features of these two conditions overlap, the ability to stratify patients by genotype or biological pathway rather than just by disease label, that is, asthma or COPD, may reveal differences in therapeutic response in clinical trials. Genetics may also increase the efficiency of outcome trials by focusing on patients at higher genetic risk of having chronic airway inflammation and tissue remodeling in response to certain exogenous stresses.

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